Looking into tablets, Characterization of pore structure in tablets using image analysis

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Chapter 7

Concluding remarks and future perspectives

The image analysis methods presented in this thesis have been shown to be valuable tools for the characterization of pore structure in tablets. They might be also applicable to other systems. In whatever setting they are to be used, care should be taken to select the appropriate filtering procedure, since sensible filtering is a prerequisite for obtaining correct results, as is explicitly shown in chapter 5. For the different analysis methods different filter procedures are used. This is a legitimate given, since the different analysis methods measure different properties, requiring a different preparation of the image. However, this does not mean that it is impossible beforehand to develop a filter routine that is suitable for all presented analysis methods. Certainly, such an 'universal' filtering procedure would make the analyses more user friendly and even wider applicable.

After reading chapter 2, 4, and 5 one might wonder which of the presented analysis methods is the best. The answer to this question is quite simple: it depends on what one wants to know. For the determination of a size distribution the most obvious choice is clearly to use the morphological sieve method. If one wants some information about the tortuosity, using the algorithm that determines the relative path length is the best option. However, the situation is more complicated for the determination of the preferential pore direction (or anisotropy in the sample). Both the quotient of the number of transitions and the relative path length could be used for this parameter. The determination of the quotient of the number of transitions is relatively simple. Results are therefore easy to understand and to check and the calculation is performed in a relatively short time on a personal computer. However, this method is very sensitive to small protrusions and tortuous structures as is discussed in chapter 6, and is therefore not so suitable when these kind of structures are observed. In those cases it might be better to apply the algorithm for the relative path length to obtain information about the preferential (pore) direction and the anisotropy in the sample.

The introduced algorithms offer a world of possibilities for (tabletting) research. For the currently presented morphological sieve method each situation should be evaluated separately concerning the parameters used for filtering, but

after sufficient calibration this technique should be widely applicable and can sometimes give even more information (location dependency) than is possible with mercury porosimetry. It should also be interesting to use the algorithm of the relative path length to investigate whether and how the relative path length of the pores (or the active drug substance) is correlated to the dissolution behavior out of a tablet. It is stated in the Higuchi equation that tortuosity is of influence, but only now a direct measure for this parameter can be determined.

In this thesis the quotient of the number of transitions has been a means to quantify anisotropy in structure, complementing work of other authors who made images of tablet structures but not quantified the anisotropy in structure. With this algorithm it has been found that the preferential pore direction in starch tablets (x-direction, see chapter 3) is different from the preferential pore direction in sodium chloride tablet (z-direction, see chapter 2). The explanation probably lies in the lower yield strength of the starch which deforms more during compression than sodium chloride at similar compaction pressures. However, it should also be investigated whether anisotropy analyzed with the relative path length gives the same results. Still, the found difference forms a good starting point for research into how the compaction behavior of excipients (and perhaps the initial powder packing and particle shape) influences the preferential pore direction in tablets and what the consequences are for (anisotropy) in mechanical strength.

It would also be interesting to expand the work done on a mixture (chapter 6) and to evaluate how the addition of a component with another compaction behavior changes the tablet structure and consequently the mechanical strength. As long as the dominating component forms a percolating system (and the other components do not), a similar experimental set up as in chapter 6 can be used. Adding more excipient(s) makes it necessary to modify the used techniques, but it would certainly be interesting.

In the future, images will probably become more and more important in the pharmaceutical industry because of the trend to build in more online steps checking the product as is the case in Process Analytical Technology (PAT). Since images offer the possibility for checking the process in a non-invasive way, they will become more important. The growing number of possibilities to obtain images (near infrared, Raman spectroscopy, x-ray tomography, several sorts of microscopy, etc.) and publications on this subject shows that this trend has already started. However, techniques for quantification in images are still limited. Techniques presented in this thesis might, in time, help contribute to fill this gap.

Summary

The internal structure of tablets influences in many aspects the product properties. Examples of such properties are the mechanical strength or the dissolution behaviour of the tablet. Not only the size, spatial distribution, and shape of the solid components are important, but also the distribution of another, widely neglected 'component': air. It is widely known that the porosity of a body affects its mechanical properties and that next to this the spatial distribution of the pores, their size and shape and their location are relevant too. Unfortunately, for the determination of pore size, assumptions regarding the pore shape are necessary. Very few techniques exist to quantify this latter property. The main problem is that the pores are not isolated entities, but are usually connected with each other. Techniques for quantifying structure and shape of interconnected entities (in tablets) are therefore introduced in this thesis. The focus lies on the pore structure in tablets, since tablets are the mostly used solid dosage form in the pharmaceutical field. However, it should be recognized that the discussed techniques might very well be applicable to other systems.

The introduced analysis techniques make use of images, since this offers the possibility to visualize the shape and structure of the pores in a location dependent manner. There are many techniques possible to obtain images. In this thesis, scanning electron microscopy (SEM) images were used, since it was found that this technique produced images with good resolution and sufficient contrast between the phase (the pores) to be analyzed and the other components (solids). These are important prerequisites for successful (image) analysis. For the quantification of structures measurement techniques inspired by both stereology and mathematical morphology are used. Stereology can be described as a body of methods for the exploration of three-dimensional space, when only two-dimensional sections through solid bodies or their projections on a surface are available. By sampling the two-dimensional sections with probes (usually points, lines or planes) information about properties of the three dimensional structure can be obtained. The mathematical basis for the used equations was laid in the 19th century. Mathematical morphology was introduced about one century later. It can be described as a collection of algorithmic tools that can be executed by a digital computer and, when applied to an image, yield a transformed image. By executing these transformations on different scales, the transformed images can be used for performing measurements.

Chapter 2 describes how the pore structure in a cubic sodium chloride compact is visualized in a location dependent manner and how the images are

analyzed to obtain the porosity and the preferential pore direction. Visualization of the pore structure is done by embedding compacts made with uni-axial compression with glycol methacrylate (GMA), which is widely used for embedding of biological specimens and subsequent sectioning. After embedding and hardening of the polymer, several planes in the compact could be imaged with SEM by scraping off appropriate quantities of the sodium chloride/polymer matrix. The nomenclature used to indicate the different planes and the different directions is also introduced in this chapter. Plan images provide a top view and are made when looking parallel to the direction of compression (z-direction). In plan images an x-direction and a y-direction are defined. Elevation images provide a side view and are made looking at the compact in the direction perpendicular to the direction of compression.

Visual inspection of the images revealed that it is possible with the used method to obtain images with sufficient resolution and a good contrast between the sodium chloride grains and the pore phase, without disrupting the pore structure. With these images the porosity at different locations in the compact could be determined. The images were made binary and the percentage of pixels in the pore phase was counted. It was found that the porosity increased with increasing tablet depth. Information about the preferential pore direction was obtained by counting the number of transitions between the salt phase and the pore phase in different directions, a method similar to the line intercept count in stereology. By taking the quotient of the number of transitions between two directions in each image, it was found that the pores were preferentially oriented in the z-direction.

The image analysis method introduced in chapter 2 is used in chapter 3 for the analysis of the preferential pore direction and its relation to the fracture behavior of compacts made of pregelatinized starch. This excipient was chosen because of the possibility to obtain compacts without any pores. It was believed that studying the fracture behavior of compacts with this extremely low porosity would make it easier to evaluate the influence of the pore structure.

Cubic starch compacts of varying porosities were made. These compacts were compressed between two flat platens in the direction parallel to the direction of the original compression (z-direction) or perpendicular to it (x-direction). By registering the force-displacement curve while doing so, the crushing force and the yield strength were measured in the x-direction and the z-direction. The previously introduced image analysis method was slightly modified to make it applicable for the measurement in the starch compact. These modifications involved an incubation with osmium tetroxide crystals for a good contrast in the images and a refinement of the segmentation procedure due to incomplete pore filling with the

resin at low porosities. The measurement of the quotient of the number of transitions was performed in filtered gray scale images instead of in binary images. This was done to make the best use of the information contained in the original images.

The crushing force in the z-direction was found to be higher than the crushing force in the x-direction, with both crushing forces decreasing with increasing porosity. Below a certain porosity the compacts did not break anymore but showed only a yield point. The height of this yield point was similar in the x-direction and in the z-direction when the porosity of these compacts was 10% or less. The results also showed that the fracture behavior was more brittle at higher porosities. The anisotropy in mechanical strength for the ductile and for the more brittle fractures correlated with an anisotropy in pore structure as image analysis showed that the pores were preferentially oriented in the x-direction. The difference in preferential pore direction between the cubic sodium chloride compacts and the starch compacts might lie in the different deformation behavior of the two excipients.

In chapter 4 the relative path length is determined in the images obtained with the method described in chapter 2. The relative path length (the path length from one side of the image to the other side divided by the length of the image) can be used as a measure for tortuosity. Tortuosity is usually defined as the ratio of the actual path length through the pores from one point to another and the shortest linear distance between these points. However, current methods for the determination of tortuosity do not calculate the path length directly. The method described in chapter 4 makes this possible. This method is based on the 'gray-weighted distance transform' that calculates the path that results in the shortest traveling time when going from a set of predefined starting points to any other point in the image. By setting the appropriate propagation speeds through the pores and over the grains, the (relative) path lengths through the pores or over the grains can be calculated, as is discussed in chapter 4. The influence of particle size of the relative path length is also investigated.

As expected it was found that the relative path length through the pores is significantly longer than the relative path length over the grains. This could be explained by the fact that the grains occupy a larger volume (70%) in the compacts than the pores (30%). In most cases, the relative path length through the pores was significantly higher for the compacts containing small particles than for the compacts made of large particles. This might be due to the larger pore size in the compacts made of the larger particle size, which offers more possibilities for cutting corners, reducing the distances traveled. Furthermore, it was possible to use this algorithm for the detection of anisotropy in the sample. The relative path

length is not completely the same as the tortuosity in compacts. However, because of the strong resemblance between these two parameters, it does provide a direct measure for the tortuosity in a compact and can be used to characterize (pore) structures.

Another technique for the characterization of structures is discussed in chapter 5. This chapter introduces a method to determine the pore size distribution in images with a morphological sieve. The (virtual) morphological sieve shows some similarities with the (real) standard laboratory sieve. With laboratory sieves a particle size distribution can be obtained by sieving a powder heap. With a morphological sieve a size distribution of structures in an image can be obtained. When the image shows pore structures, a pore size distribution can thus be obtained. Chapter 5 describes the underlying principle of the morphological sieve which is based on standard operations used in mathematical morphology. The used filtering procedure is explained and the influence on the pore size distribution of the removal of small cracks and small 'floating' grains (i.e. not connected to the rest of the grain matrix) is evaluated. The resulting pore size distribution is compared to the pore size distribution obtained with mercury porosimetry.

Small 'floating' particles prevented the detection of large pores, but had negligible effect on the porosity. Since it is impossible that such grains would occur in the real physical situation they needed to be removed before the determination of the pore size distribution. Small cracks inside the grains hardly affected the pore size distribution, but had a large effect on the found porosity. Since these cracks are induced by the sample preparation or are already accounted for in the true density of the sodium chloride, they should also be removed. The choice for the maximum size of the structures to be removed was based on the comparison between the porosities after removal and the experimentally determined porosity.

The resulting pore size distributions were compared to the pore size distributions obtained with mercury porosimetry. The shapes of the curves found by both methods were different. This was caused by different assumptions on pore shape. Mercury porosimetry assumes a cylindrical pore shape. The morphological sieve method assumes that the pores are spheres being cut through their centre, resulting in a broader size distribution with slightly smaller pores than the real physical size distribution. However, both methods could make a distinction between the pore size distributions of the tablets made of the different particle sizes and the results of both methods were in the same order of magnitude. Therefore, it could be concluded that the morphological sieve method is a suitable alternative for mercury porosimetry for the (size) characterization of (pore) structures in images.

The different methods introduced in chapters 2, 4, and 5 are used in chapter 6 to test the hypothesis that the addition of a minor component causes a change in pore shape in the matrix of the primary component. This was done since it was found in a previous research project on binary mixtures that the addition of a small amount of starch caused a significant decrease in the strength of a sodium chloride matrix, a decrease larger than expected upon interpolation. It was hypothesized that a change in pore shape in the sodium chloride matrix was the cause of this decrease in strength. In order to test this hypothesis tablets made of sodium chloride only and tablets made of a mixture of sodium chloride (97.5% v/v) and starch (2.5% v/v) were compared. A heat treatment was used to remove the starch. In this way the pore structure could be assessed before and after the addition of starch. Next to the techniques introduced in the previous chapters, mercury porosimetry was used.

At comparable porosities the tensile strength of the mixture tablets was significantly lower than that of the tablets made of NaCl only. Visual inspection of the images with the naked eye suggested a lower connectivity of the grains for the heat treated mixture. This was confirmed by the results of the algorithm calculating the relative path length. The algorithm for the quotient of the number of transitions did not indicate a difference in pore structure between the different tablets. Mercury porosimetry did neither indicate a difference in pore size distribution. However, the morphological sieve method showed that the pore size distribution shifted towards a larger pore size after the addition of starch. The lower mechanical strength of the tablets made of the binary mixture was thus caused by the lower connectivity of the grains and more larger pores as could be detected with the image analysis methods.